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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,004	11/21/2003	Nancy L. Haigwood	SBRI 122224	9077

57277 7590 10/06/2006

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,004	HAIGWOOD, NANCY L.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December, 2004,* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/19/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Office Action

Status of the Claims

Claim 1 is the only pending in the instant application.

37 C.F.R. § 1.98

The information disclosure statement filed 19 December, 2005, has been placed in the application file and the information referred to therein has been considered.

Applicant is advised that the listing of references in the specification is not a proper information disclosure statement. 37 C.F.R. § 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and M.P.E.P. § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited or considered by the examiner on a form PTO-892 or PTO-1449, they have not been considered.

37 C.F.R. § 1.57(d)

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see p. 8). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See M.P.E.P. § 608.01.

35 U.S.C. § 112, Second Paragraph

Claim 1 is rejected under 35 U.S.C. § 112, second paragraph,

as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Two separate requirements are set forth under this statute: (1) the claims must set forth the subject matter that applicants regard as their invention; and (2) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. The reference to a "vaccination protocol" is vague and indefinite since the purpose of this protocol is not readily manifest. For instance, is the vaccination protocol directed toward the induction of an HIV-1-specific immune response in humans or non-humans? Is the protocol directed toward the induction of an HIV-1-specific neutralizing antibody response, helper T-lymphocyte response, or cytotoxic T-lymphocyte response (CTL)? Applicants should clearly and unambiguously set forth the purpose of the protocol in the preamble (i.e., A vaccination method for the induction of a protective/therapeutic HIV-1-specific neutralizing antibody response) and provide a conclusory statement (i.e., wherein said protocol results in the induction of a protective/therapeutic HIV-1-neutralizing antibody response). The reference to an "HIV envelope immunogen" is also confusing. The term HIV could encompass HIV-1, -2, or both -1 and -2. A review of the specification would suggest the focus of the invention is the HIV-1 envelope glycoprotein. There does not appear to be any discussion directed toward the HIV-2 envelope and changing glycosylation patterns. Appropriate amendment of the claim language is required (i.e., HIV-1 envelope immunogen). Finally, the reference to a "minimum number of N- and O-linked glycosylation sites" is vague and indefinite since it is not readily manifest how many glycosylation sites must be present in

the envelope immunogen. The HIV-1 envelope on average contains between 19 and 23 glycosylation sites depending upon the isolate. Simply referencing a minimum number of sites does not allow the skilled artisan to ascertain the metes and bounds of the claimed subject matter. How many glycoslyation sites does the immunogen contain? Appropriate correction is required.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim is directed toward a vaccination protocol that employs a first HIV envelope immunogen containing fewer N- and O-linked glycosylation sites as compared to a second HIV envelope immunogen. The first envelope is used in the primary vaccination whereas the second envelope is used in one or more booster immunizations. The invention is predicated upon the discovery that an SHIV virus carrying an HIV-1 envelope displayed increased neutralization resistance. This resistance was associated with the addition/removal of additional glycosylation sites. Presumably the addition of these sites provided a glycan shield that

protected the virus from neutralizing antibodies.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide sufficient guidance pertaining to those N- and O-linked glycosylation sites that are required for the induction of protective or therapeutic immune responses. The prior art clearly demonstrates that glycosylation patterns have different effects on envelope neutralization depending upon the clade, strain, isolate, and time of isolation (Song et al., 2004). However, the claims simply require a "minimum number" of glycosylation sites yet the specification fails to clearly identify the minimum structural requirements that are required for a protective or therapeutic immune response. In fact, a recent study by Song and colleagues actually demonstrated that addition of an N-linked glycosylation site in the gp41 ectodomain contributed to neutralization sensitivity, contrary to the findings set forth in this

application. An additional study by Quińones-Kochs *et al.* (2002) reported that while Env mutants lacking glycosylation sites were more sensitive to neutralization, nevertheless, they were no more efficient at inducing neutralizing antibodies than wildtype virus. Teeraputon and colleagues (2005) generated a number of Env mutants with defective glycosylation sites and noted that some led to increased neutralization sensitivity whereas others had no effect on the neutralization phenotype. The specification is silent concerning these findings.

2) The disclosure fails to provide any guidance pertaining to the correlates of human protection. One of the continuing problems with HIV vaccine development has been the failure to identify those human correlates that are associated with a protective or therapeutic immune response. At present it is not known if a humoral, cell-mediated, or both humoral and cell-mediated immune responses are required for protection. The specificity, titer, and duration of any given immune response that is required for protection remains to be elucidated. Thus, even if the disclosed modified envelopes were actually employed in an immunization regimen, the skilled artisan could not reasonably ascertain if those result are relevant to achieving protection in the clinic.

3) The disclosure fails to provide any guidance pertaining to the quasispecies nature of HIV infection and how this leads to immune escape and evasion. The quasispecies nature of HIV infection has been well-documented (Haynes, 1996). HIV is capable of generating up to 10^9 new virions per day which leads to a large population of genotypically/phenotypically distinct viruses even within the same individual. This vast genetic variation quickly leads to the identification of neutralization-resistant variants. Moreover, the vast heterogeneity of these

viruses also necessitates that any given vaccine must be able to neutralize both homologous and heterlogous isolates. The disclosure fails to provide any guidance pertaining to this issue.

4) The state-of-the-art, as it pertains to HIV vaccine development, is one of unpredictability and continued failure. Several envelope-based vaccines have already undergone clinical trials and all have failed to induce protective or therapeutic immune responses in humans. There are several problems associated with HIV vaccine development including the following: (1) a lack of understanding of the correlates of human protection, (2) criteria for selection of suitable vaccine strains, (3) the identification of suitable immunogens that are capable of inducing broad neutralizing antibodies, (4) the identification of suitable immunogens that are capable of inducing CTL responses to multiple conserved epitopes in human populations with diverse MHC backgrounds, (5) the ability to induce effective mucosal immune responses where virus is normally transmitted, (6) the quasispecies nature of HIV infection which leads to immune escape and evasion, (7) the ability of HIV to establish latency, (8) and the lack of an adequate animal model that is reasonably predictive of vaccine efficacy (Mooij and Heeney, 2002; Piguet and Trono, 2001; Haynes, 1996; Kohler *et al.*, 1992; Moore and Burton, 1999; Feinberg and Moore, 2002; Staprans and Feinberg, 2004; Gallo, 2005; Nishimura *et al.*, 2004). The disclosure fails to address any of these caveats.

5) The disclosure fails to provide any working embodiments. The data provided in the specification was obtained from an SHIV primate model and does not constitute a proper working example. First, the specification did not perform any immunogenicity

studies wherein the modified envelopes were used to prime and boost a suitable host. Data has already been provided by the examiner demonstrating that HIV-1 Env mutants that lack one or more N-linked glycosylation sites are not more efficient at generating cross-neutralizing antibody responses than wildtype envelopes. Second, the specification failed to demonstrate that the modified envelope compositions were capable of inducing an immune response of sufficient titer and duration that would lead to a protective or therapeutic immune response. Third, the SHIV animal model, while useful for studying vaccine concepts, nevertheless is not predictive of clinical efficacy. As noted supra, there are several differences between the SHIV model and HIV infection in the clinic. At this point in time, direct extrapolations between the two systems cannot be performed. Therefore, the response to any data obtained from the SHIV model concerning protective or therapeutic immune responses must be tempered until the system is validated by clinical trials.

When all the aforementioned factors are considered in toto, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Non-statutory Double Patenting

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645

(Fed. Cir. 1985); and *In re Goodman*, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/096,698. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). *In re Berg*, 140 F.3d 1428, 46 U.S.P.Q.2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. The claim in the instant application is directed toward a vaccination protocol that employs a genus of modified HIV envelope glycoproteins. The claim in the '698 application is directed toward the same vaccination protocol but employs a species of modified HIV envelope. Accordingly, the claim in the '698 application would anticipate the instantly claimed invention. This is a **provisional** obviousness-type double

patenting rejection because the conflicting claims have not in fact been patented.

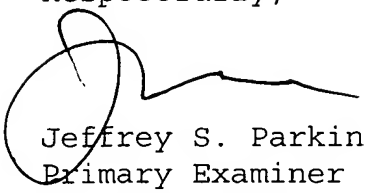
Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,



Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

26 September, 2006